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Determinants of daily insulin use in Type 1 diabetes

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Abstract

Objective: Insulin need for a given degree of glucose control varies markedly among individuals. We examined which factors determine daily insulin use in patients with Type 1 diabetes. **Methods:** A cross-sectional study was performed in 416 patients. Clinical parameters, medication use, physical activity, smoking, alcohol consumption, and laboratory parameters were determined. **Results:** Body mass index and waist circumference were positively related to daily insulin use (2.3 U/kg/m^2, 95% CI=1.9–2.7 and 0.8 U/cm, 95% CI=0.6–0.9, adjusted for age and sex). Age, female sex, and duration of diabetes were inversely related to daily insulin dose. There was an increase of 3.6 U of insulin per mmol/l triglycerides (95% CI=1.04–6.2) and a decrease of 5.9 U of insulin per mmol/l high-density lipoprotein cholesterol (95% CI=−10.0 to −1.8), adjusted for age, sex, and weight. For blood pressure-lowering drugs, the strongest relation was found for thiazide diuretics (difference of 7.1 U insulin/day, 95% CI=0.2–14.2, adjusted for age, sex, and weight). The use of an insulin pump and physical activity were related to lower daily insulin need: −8.7 U/day (95% CI=−11.8 to −5.5) and −1.7 U/day per activity score unit (95% CI=−3.2 to −0.2), respectively, adjusted for age, sex, and weight. Smoking was related to an increased need of 5.3 U/day (95% CI=1.5–9.0), adjusted for age, sex, and weight. **Conclusions:** Our results show that components of the metabolic syndrome are positively related to daily insulin use. Also, decreased physical activity, smoking, and the use of blood pressure-lowering drugs, which influence insulin sensitivity, are associated with an increased insulin need. These findings suggest that the presence of insulin resistance in Type 1 diabetes or “double diabetes” plays a key role in determining daily insulin need.

Keywords: Type 1 diabetes; Metabolic syndrome; Insulin; Double diabetes; Insulin sensitivity; Insulin resistance; Insulin pump; Insulin injections

1. Introduction

The importance of glucose control in diabetes mellitus is firmly established. Since the Diabetes Control and Complications Trial (DCCT) in Type 1 diabetes and the UK Prospective Diabetes Study (UKPDS) in Type 2 diabetes have shown that long-term diabetic complications are reduced by improved glycemic control (DCCT Research Group, 1993; UKPDS, 1998), the target value of hemoglobin A_{1c} (HbA_{1c}) has been steadily lowered. As a result, insulin treatment is intensified in Type 1 diabetes and insulin is used in an increasing proportion of patients with Type 2 diabetes. Apart from the clear beneficial effect of glucose-lowering, insulin treatment results in weight gain, increases the risk of acquiring hypoglycemia, and affects quality of life (DCCT Research Group, 1993; Purnell et al., 1998). Moreover, insulin is an anabolic hormone that in experimental studies has shown to induce atherogenic effects (Muis, Bots, Grobbee, & Stolk, in press; Vicent et al., 2003). Finally, insulin treatment is expensive. In Type 1 diabetes, the daily insulin need ranges markedly per individual from 0.4 to

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0.85 U/kg/day (DCCT Research Group, 1993). Information on the factors associated with insulin need may point to possibilities for avoiding unnecessarily high insulin use.

In this light, we set out to investigate the determinants of insulin use in individuals with Type 1 diabetes. In addition to glucose control, body composition and physical activity may also affect an individual's insulin needs. In this study, we examined lifestyle and other determinants of daily insulin use.

2. Methods

2.1. Study population

A study was performed on 416 patients with Type 1 diabetes mellitus. Patients were recruited from the outpatient clinics of the Isala Clinics (Zwolle, the Netherlands) and the Groene Hart Hospital (Gouda, the Netherlands). Type 1 diabetes mellitus was defined as onset at an age younger than 40 years in combination with insulin dependence from diagnosis. The main inclusion criteria for enrollment were age $\geq$18 years and duration of insulin treatment of at least 4 years. Of the 563 patients invited to participate in the study, 416 responded. The 147 nonresponders did not significantly differ from the responders in major determinants (age, sex, duration of diabetes, and family history).

The medical ethics committees of the participating institutions approved the study, and all patients gave their written informed consent.

2.2. Clinical parameters

The patients were examined according to a standardized protocol. Patients were asked to complete a questionnaire on physical activity (estimated by the modified Baecke questionnaire; Pols et al., 1995) at home. Alcohol consumption, smoking habits, use of medication including the actual daily insulin dose, medical history including duration of diabetes and diabetic complications, and family history for CVD, hypertension, lipid disorders, and diabetes mellitus were recorded during the visit at the research center. Blood pressure was measured three times on the left arm with a semiautomated device (Dynamap) in the supine position. Height, weight, and waist circumference were measured and body mass index (BMI; kg/m^2) was calculated. The averages of the latest available levels of glycosylated HbA$_{1c}$ total serum cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides (TGs), microalbumin, and creatinine from 2 years preceding study inclusion were obtained from the patients' medical files.

2.3. Physical activity

To assess daily physical activity (DPA), we used a modified Baecke questionnaire for physical activity (Pols et al., 1995). This questionnaire has been validated for the Dutch population. The questionnaire consisted of scores in work activities, sports activities, and other leisure time activities that were added up to give the DPA score. Items on each activity were questions with five possible ratings, ranging from *inactive* to *very active*. Scores in sports and other activities were calculated from type of activity and the duration and period of the year in which the activity was normally performed. All activities were classified according to work, posture, and movements. An intensity code was used to classify each type of activity. The higher the activity score, the more active a patient was.

2.4. Data analysis

Data are summarized using means and standard deviations or proportions. The relations between daily insulin use and the different parameters were evaluated using univariate and multivariate linear regression analyses. Adjustments were made for differences in age, sex, and weight where appropriate. Total daily insulin use was used as a continuous variable in the analysis. The analyses were repeated for the daily use of the specific types of insulin (short-acting analogues, regular insulin, and intermediate-acting insulin). In addition, we performed analyses separately for men and women and for patients using an insulin pump. Data were analyzed using SPSS 10.1 for Windows.

Table 1
General characteristics of the study population

	Men	Women
n	222	193
Age, years [mean (S.D.)]	45.8 (12.6)	40.3 (11.8)
Duration of diabetes, years [mean (S.D.)]	22.0 (12.2)	19.7 (10.6)
Family history of diabetes–Types 1 and 2 (%)	31	30
BMI, kg/m^2 [mean (S.D.)]	25.4 (3.5)	25.7 (3.8)
Obesity–BMI>27 kg/m^2 (%)	28	32
Physical activity[a] [mean (S.D.)]	7.7 (1.1)	7.8 (1.1)
Alcohol use, g [mean (S.D.)]	16.8 (22.8)	7.0 (10.1)
SBP, mm Hg [mean (S.D.)]	144.7 (20.8)	133.9 (20.0)
DBP, mm Hg [mean (S.D.)]	83.0 (9.8)	80.9 (10.1)
HbA$_{1c}$, % [mean (S.D.)]	7.9 (1.0)	7.9 (0.9)
Total cholesterol, mmol/l [mean (S.D.)]	4.9 (0.9)	5.1 (0.9)
TGs, mmol/l [mean (S.D.)]	1.0 (0.5)	1.0 (0.7)
HDL cholesterol, mmol/l [mean (S.D.)]	1.4 (0.4)	1.8 (0.4)
Proportion using ACE inhibitors (%)	18	11
Proportion using calcium-channel blockers (%)	3	3
Proportion using β-blockers (%)	6	4
Proportion using thiazide diuretics (%)	4	6
Proportion using lipid-lowering drugs (%)	13	7
Daily insulin dose, IU/day [mean (S.D.), range]	55.0 (21.6), 4–128	44.7 (16.9), 11–106
Pump use (%)	36	62
Current smoking (%)	29	19

SBP indicates systolic blood pressure; DBP, diastolic blood pressure.
[a] Measured by the modified Baecke questionnaire.

3. Results

The general characteristics of the 416 patients included in the study are presented in Table 1. The mean age of the patients was 43.2±12.5 years, and the mean duration of their diabetes was 20.9±11.5 years. Of all the patients, 304 (73%) used short-acting analogues, 112 (27%) used regular insulin, 217 (52%) used intermediate-acting insulin, and 199 (48%) were treated with an insulin pump. In the group of patients who were treated with an insulin pump, 12% used regular insulin whereas 88% used short-acting analogues.

The relations between clinical and biochemical parameters and daily insulin use are presented in Table 2. As expected, HbA_{1c} levels were positively related to daily insulin dose (2.2 U of insulin per %, 95% CI=0.3–4.1), adjusted for sex and age. This relation was stronger in women than in men (3.4 U of insulin per %, 95% CI=0.9–6.0 and 1.4 U of insulin per %, 95% CI=−1.3–4.1, respectively). Age was inversely related to daily insulin dose (decrease of −0.4 U of insulin/year, 95% CI=−0.5 to −0.2). Fig. 1 shows daily insulin dose by increasing age. TGs were positively related to daily insulin use (increase of 7.0 U of insulin per mmol/l, 95% CI=4.1–9.9), adjusted for sex and age. Likewise, HDL cholesterol was inversely related to daily insulin use (decrease of −9.8 U of insulin per mmol/l, 95% CI=−14.5 to −5.1). The associations for TG and HDL with insulin attenuated when additional adjustment for weight was performed but remained statistically significant (Table 2). Physical activity was inversely related to insulin use, after adjustment for age, sex, and weight (decrease of −1.7 U of insulin per score unit, 95% CI=−3.2 to −0.2).

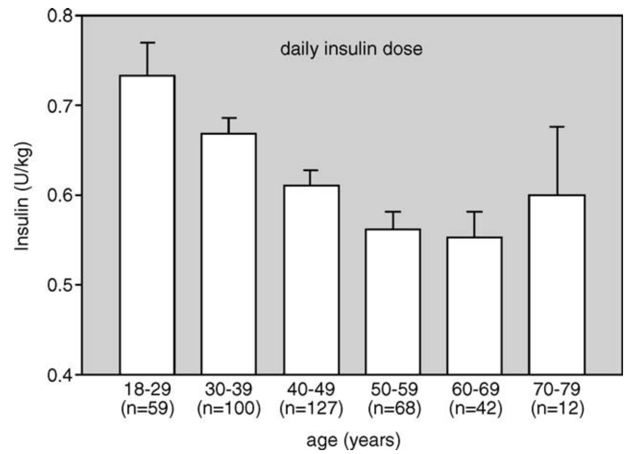

Fig. 1. Daily insulin dose by increasing age.

Pump users needed less daily insulin than patients using multiple injections (difference of −9.3 U of insulin/day, 95% CI=−13.0 to −5.5). The analyses were repeated for patients using an insulin pump. In this subgroup, results were the same as those in the complete study population. Similar relations were found when the analyses were repeated separately for both sexes and for patients with and those without a family history of diabetes.

The use of calcium-channel blockers, β-blockers, and thiazide diuretics was related to higher total daily insulin doses (respective difference of 12.7 U of insulin, 95% CI=1.9–23.5; 8.3 U of insulin, 95% CI=−0.03–16.7; and 10.4 U of insulin, 95% CI=2.4–18.3), adjusted for sex and age. When weight was taken into account, the magnitude of the association attenuated but remained statistically signifi-

Table 2
Association of clinical and biochemical parameters and daily insulin dose

	Adjusted for age and sex	Adjusted for age, sex, and weight
Age, years	−0.4 (−0.5 to −0.2)**	−0.4 (−0.5 to −0.2)**
Female sex	−13.0 (−16.7 to −9.2)**	−5.1 (−8.6 to −1.7)**
BMI, kg/m^2	2.3 (1.9–2.7)**	
Waist circumference, cm	0.8 (0.6–0.9)**	
Duration of diabetes mellitus, years	−0.2 (−0.4 to −0.01)**	−0.1 (−0.3–0.05)
Family history of diabetes–Types 1 and 2, %	0.3 (−4.2–4.8)	0.2 (−3.6–3.9)
SBP, mm Hg	0.09 (−0.008–0.2)*	0.02 (−0.07–0.1)
DBP, mm Hg	0.1 (−0.05–0.3)	−0.02 (−0.2–0.1)
HbA_{1c}, %	2.2 (0.3–4.1)**	1.5 (−0.1–3.1)*
Total cholesterol, mmol/l	1.3 (−0.9–3.4)	0.5 (−1.4–2.3)
TGs, mmol/l	7.0 (4.1–9.9)**	3.6 (1.04–6.2)**
HDL cholesterol, mmol/l	−9.8 (−14.5 to −5.1)**	−5.9 (−10.0 to −1.8)**
Physical activity	−1.1 (−2.8–0.7)	−1.7 (−3.2 to −0.2)**
Pump use	−9.3 (−13.0 to −5.6)**	−8.7 (−11.8 to −5.5)**
Current smoking	1.5 (−2.8–5.8)	5.3 (1.5–9.0)**
Alcohol use, g	−0.03 (−0.1–0.07)	−0.01 (−0.1–0.08)
Use of ACE inhibitors	3.5 (−1.8–8.7)	3.5 (−1.0–8.0)
Use of calcium blockers	12.7 (1.9–23.5)**	8.8 (−0.5–18.1)*
Use of β-blockers	8.3 (−0.03–16.7)*	1.5 (−5.9–8.8)
Use of thiazide diuretics	10.4 (2.4–18.3)**	7.1 (0.2–14.2)**
Use of lipid-lowering treatment	0.3 (−6.1–6.7)	−2.8 (−8.3–2.7)

Values are expressed as linear regression coefficients, adjusted for sex and age (if appropriate) and weight, with 95% CIs in parentheses, and reflect changes in insulin units.

* $P<.10$.

** $P<.05$.

Table 3
Association of blood pressure-lowering drugs and total daily insulin use

	BMI≤25.2	BMI>25.2
	Daily insulin use changes (U)	Daily insulin use changes (U)
Use of thiazide diuretics	15.3 (2.6–28.1)*	4.8 (−4.4–14.1)
Use of calcium blockers	16.1 (3.6–28.5)*	3.7 (−10.1–17.5)
Use of β-blockers	7.7 (−1.8–17.2)$^{P=.11}$	−3.3 (−14.5–8.0)
Use of ACE inhibitors	1.5 (−4.1–7.1)	5.8 (−1.5–13.1)

Values are expressed as linear regression coefficients, with 95% CIs in parentheses, and reflect changes in insulin units. BMI of 25.2 represents the median value.

* $P<.05$.

Table 4
A multivariate linear regression model of determinants of total daily insulin use

Age, years	− 0.4 (− 0.6 to − 0.3)*
Female sex	− 4.8 (− 8.5 to − 1.1)*
Weight, kg	0.7 (0.6–0.8)*
HbA_{1c}, %	1.2 (− 0.6–3.1)
TGs, mmol/l	3.4 (0.7–6.0)*
Current smoking, %	4.0 (− 0.02–7.9)$^{P=.051}$
Physical activity score	−1.4 (−3.0–0.1)$^{P=.069}$

Values are expressed as linear regression coefficients, with 95% CIs in parentheses, and reflect changes in insulin units. R^2=.41 (adjusted R^2=.40).
* P<.05.

cant for thiazide diuretics. The relation of the antihypertensive drugs with daily insulin use was more pronounced in patients with a BMI ≤25.2 (median; Table 3). The relations of clinical and biochemical parameters and daily doses of the specific types of insulin were in magnitude similar to the relations found for these parameters and the total daily insulin dose. Table 4 presents the results of a multivariate linear regression model built with the several determinants of total daily insulin dose. To evaluate as to which extent daily insulin use is explained by these factors, we estimated the explained variance (R^2), which was 40%. Additional adjustment in this model for the several blood pressure-lowering drugs did not change the relations. Finally, we excluded patients using comedication, which did not materially change the results. Also, additional adjustment for HbA_{1c} did not change the results.

4. Discussion

The results of this study on 416 patients with Type 1 diabetes show that BMI, waist circumference, smoking, HbA_{1c}, TGs, and the use of several blood pressure-lowering drugs are positively related to daily insulin dose. Age, female sex, duration of diabetes, HDL cholesterol, physical activity, and insulin pump use are inversely related to daily insulin need. Moreover, the use of an insulin pump resulted in a 14% lower insulin need.

To appreciate the results of this study, some issues need to be addressed. Because all measurements are performed at the same point in time in a cross-sectional design, cause–consequence relations could not be explored. Furthermore, daily insulin use was determined at one point in time whereas day-to-day variation in insulin use may be greater than the variance in several metabolic and clinical variables, including the prescription of medication. This might have led to some misclassification, which is assumed to attenuate the associations under study.

Insulin resistance is associated with the need for higher insulin doses (Henry et al., 1993; Yki-Jarvinen et al., 1997). The independent effect of body weight and TG levels on daily insulin dose is in line with studies suggesting that these are markers of insulin resistance and are, therefore, associated with higher insulin use. Our findings for HDL cholesterol agree with this view. Patients with Type 1 diabetes may also suffer from the metabolic syndrome, which is sometimes referred to as “double diabetes” (Libman & Becker, 2003). Furthermore, it is well known that intensified insulin treatment may result in weight gain (Diabetes Care, 2001), which, on the other hand, may partly explain our findings.

Some of our findings on the impact on insulin need of blood pressure-lowering drugs agree with previous reports (Luna & Feinglos, 2001). β-Blocking agents are known to slightly deteriorate glucose metabolism (Mills & Horn, 1985; Wicklmayr, Rett, Dietze, & Mehnert, 1990), probably through reducing peripheral insulin sensitivity (Jacob et al., 1996). Our findings show a borderline significant relation between β-blocking agents and insulin use. Diuretics, especially thiazide diuretics, may also cause glucose intolerance (Helderman et al., 1983), primarily through the reduction in total body potassium and subsequent decreased insulin secretion. To our knowledge, this is the first study to show that the use of thiazide diuretics is positively related to daily insulin use in Type 1 diabetes (difference of 10.4 U, P=.01; Table 2).

Furthermore, we found that calcium-channel antagonists were positively related to daily insulin use (difference of 12.7 U, P=.02; Table 2); however, this is in contrast with findings by other investigators. Published work suggests that at hemodynamically active doses, calcium antagonists do not interfere with glucose tolerance (Collins, Cullen, & Feely, 1987). The relation of calcium antagonists and insulin sensitivity or glucose metabolism is less clear.

The relation of most of the antihypertensive drugs with daily insulin use was more pronounced in patients with a BMI ≤25.2 (Table 3). This supports the hypothesis that these drugs induce insulin resistance, an effect that may be more evident in patients with a normal BMI, thus with less insulin resistance. Evidence sustaining the theory of drug-induced insulin resistance is to be found in the results obtained from the multivariate model (Table 4) built with several determinants of the metabolic syndrome, in which additional adjustment for the blood pressure-lowering drugs did not change the relations. This may well be explained by the causal relationship between determinants of insulin resistance and antihypertensive drugs.

An alternative explanation for an association between daily insulin need and blood pressure-lowering drugs would be the well-documented relation of blood pressure levels with components of the metabolic syndrome that, as indicated above, may well be present in some patients with Type 1 diabetes. Finally, a relation between antihypertensive drugs and insulin use could result from “confounding by indication” (Grobbee & Hoes, 1997). As higher insulin use is related to worse control and increased risk of complications, these patients may well need using blood pressure-lowering medication for that reason. However, additional adjustment for HbA_{1c} levels did not change the relations we found. This argues against the hypothesis of “confounding by indication.”

Chronic cigarette smoking is associated with increased insulin resistance and could, therefore, lead to a higher insulin need (Targher et al., 1997). This has also been shown in experimental studies where cigarette smoking acutely impaired insulin action (Attvall, Fowelin, Lager, Von Schenck, & Smith, 1993; Frati, Iniestra, & Ariza, 1996). Another study found a significant improvement in HbA_{1c} levels (0.7% decrease) after smoking cessation in 34 subjects with diabetes (Gunton, Davies, Wilmshurst, Fulcher, & McElduff, 2002). These findings are in line with those of our study.

A reduced need for insulin in patients using an insulin pump for continuous subcutaneous insulin infusion (CSII) is evident. It is known that the use of CSII decreases the amount of daily insulin dose by at least 14% (Pickup, Mattock, & Kerry, 2002). In our study, we found a difference of −9.3 U (18.5%) of the mean daily insulin dose between patients using and those not using CSII.

Age and duration of diabetes were inversely related to insulin need (Fig. 1). The relation of age with daily insulin use is most likely caused by selective nonresponse. Patients with a higher insulin dose have possibly an increased risk of acquiring diabetic complications and will get disabling diseases at an earlier age.

Physical exercise is known to increase insulin sensitivity and decrease insulin need (Kemmer, 1992; Peirce, 1999). In our study, this association was only significant after adjustment for weight, which may indicate that body weight is a stronger determinant of insulin use than physical activity. Another explanation may be that patients with Type 1 diabetes do more easily gain weight than get exercise.

In conclusion, we found that several components of the metabolic syndrome, such as high TGs, low HDL cholesterol, and increased BMI, are positively related to daily insulin use in Type 1 diabetes. Furthermore, our results show that decreased physical activity, smoking, and the use of antihypertensive drugs are associated with an increased insulin need. The findings of our study suggest that the presence of insulin resistance in Type 1 diabetes plays a key role in determining daily insulin need.

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